REMARKS

The courteous interview extended to one of the applicants and the applicants' representative by Examiner Travers on December 9, 2002, is acknowledged with appreciation. During the interview, the Examiner suggested the claims be more focus on the specific problems solved by the present invention and the independent claim has been so amended. The opening paragraphs of the application point out that one of the undesirable side effects of estrogen treatment is bleeding and that while SERM treatment will obviate that problem for a short period of time, the estrogen side effect will reappear. The present invention is designed to modulate the side affects of the SERM treatment and to do so, used is an agent which exhibits progestogenic activity. Such agents have their own side effects when used for contraceptive purposes, and particularly are characterized by breakthrough bleeding. The invention is based on the fact that there is an amount of the progestogenic agent which is effective to modulate the bleeding side effect of the SERM without contributing its own bleeding problem while permitting the SERM to be used as a contraceptive. This is neither taught nor suggested in the prior art.

The last Office Action in the parent case set forth a number of rejections. It is respectfully submitted that those rejections should not be repeated.

First, the specification was objected to under the first paragraph of 35 U.S.C. 112 for failing to provide an enabling disclosure and the claims were rejected under the first and second paragraphs of Section 112. While the rejection based on the second paragraph was phrased in terms of being indefinite concerning the SERM and progestogenic agent, other statements in the Office Action correctly acknowledge that those skilled in the art know what such SERM and progestogenic agents constitute and therefore, the terms are not indefinite. It is clear, therefore, that this rejection is also based on enablement. While it is believed a question of enablement was not valid for

the reasons stated in earlier responses, it is respectfully submitted that the enablement rejection has been obviated by the foregoing amendment. The use of SERM for contraception is known and therefore that aspect of the claims is clearly enabled. What constitutes a progestogenic agent is also known and that fact coupled with the description of typical agents in the application provides enablement. Typical amounts used in connection with the specific agents are also disclosed in the application and, moreover, can be easily determined by those skilled in the art without undue experimentation. It is therefore respectfully submitted that the full scope of the claims as amended is fully enabled.

The last Office Action in the parent case also advanced a rejection under 35 U.S.C. 103 over Jones, Basu and Schane. The Jones and Basu references were cited to show the use of SERMs in connection with contraception. Jones is concerned with birds, rodents and small animals while Basu is concerned with mice, rats and rabbits. Nevertheless, Applicants acknowledge that those references reflect early beliefs about SERMs. However, it became known that such beliefs did not extend to humans in that it was determined later that the SERMs were fertility agents in premenopausal women. See Clark, of record. [A copy of the first article (Greenblat et al., JAMA 178: 101) demonstrating that clomiphene (MRL 41) induced ovulation in women and discussing the contrast between rats and women is enclosed for the Examiner's information.] It was found that over time, the SERM caused "run away" endogenous estrogen production causing ovulation in addition to exaggerating the estrogen side effects. At the time of the present invention, use of a SERM for contraceptive purposes was contraindicated.

The Schane patent was cited to show a particular progestogenic agent as an oral contraceptive. In the human female, however, progestins are well known to induce

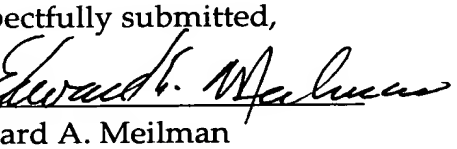
bleeding. It makes no sense to add use of an agent which induces bleeding to the use of a material which is also known to be characterized by a bleeding side effect (the SERM).

The presently claimed invention is based on the progestogenic agent counteracting the known attributes of the SERM in two ways. First, it permits the SERM to be used as an anti-fertility agent (as originally proposed in, e.g., Jones and Basu), thereby returning the SERM to usability as a contraceptive agent. Second, it modulates the bleeding side affect of the SERM. There is no teaching or suggestion anywhere in the prior art to the effect that there is an amount of a material known normally to induce bleeding which will counteract the bleeding side affect of another material. Nothing in the prior art suggests the two agents can be used as claimed herein.

Accordingly, it is respectfully submitted that this application is in condition to be allowed and the early issuance of a Notice of Allowance is respectfully requested.

Dated: June 27, 2003

Respectfully submitted,

By 

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Induction of Ovulation with MRL/41*

Preliminary Report

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MRL/41, an analogue of the nonsteroid estrogen, chlorotrianisene, was evaluated in the human female because it was shown to possess pituitary gonadotropin-inhibiting and antifecundity properties in rats. Although structurally related to a hormone-like chemical agent, this compound does not exhibit estrogenic, progestogenic, or androgenic activity in the human. Studies with this drug were initiated primarily because of its potential as an antifertility agent. Contrary to expectations, some unsuspected and interesting biological activities were observed, one of which was the induction of ovulatory-type menses in amenorrheic anovulatory females.

UNEXPECTED and interesting biological activity in the field of reproductive physiology was encountered while evaluating an experimental compound, MRL/41 (1-[*p*-(*β*-diethylaminoethoxy)phenyl]-1,2-diphenyl-2-chloroethylene), as an infertility agent in women. In the rat, this compound has been known to have pituitary gonadotropin-inhibiting and antifecundity properties,[1] but such attributes were not, to us, the most interesting areas of study. Instead, MRL/41 was found to possess a surprising potential for the induction of ovulatory-type cycles in amenorrheic women. A related compound, MER-25 (1-[*p*-2-diethylaminoethoxyphenyl]-1-2-*p*-methoxyphenylethanol), has also been reported to initiate ovulation.[2]

Induction of ovulation is one of the areas in human reproduction in which investigative efforts have met with meager success. The finding that MRL/41, a nonsteroid chemical agent, is capable of inducing presumable** ovulation in a high percentage of amenorrheic women is a most welcome development in this difficult field of endeavor.

Materials and Methods

MRL/41 is structurally related to the synthetic nonsteroid estrogen, chlorotrianisene (Tace). The citrate salt of MRL/41 was employed in 25- to 50-mg. doses administered 2 or 3 times per day for periods ranging from 8 days to 8 months. The patients were instructed to keep daily basal temperature records (BTR). Studies were undertaken to determine changes in vaginal cytology, cervical mucus, and endometrium. Hormone assays were obtained when feasible. These included determinations for urinary gonadotropin, 17-ketosteroids, 17-ketogenic steroids, and pregnanediol. The effect of the compound was studied in 4 normal ovulatory women, in 3 girls with precocious puberty, and in 43 amenorrheic women in the reproductive age range. Complete blood counts, urine analyses, and liver function tests were performed in those given prolonged treatment.

Normal Ovulatory Women.—MRL/41 was administered to 4 women with normal ovulatory cycles to see if this agent could inhibit pituitary gonadotropin and thus prevent ovulation. Inhibition of ovulation was not apparent in any of the 4 cases, but in 2 there was delay of menses, and the thermogenic effect of the corpus luteum was sustained for periods of 20 and 25 days instead of the usual 14-day postovulatory elevation.

From the Department of Endocrinology, Medical College of Georgia.

*The adopted non-proprietary name is clomiphene citrate.

**It is realized that the only true criteria for ovulation are the recovery of ova or the occurrence of pregnancy.

Precocious Puberty.—Three girls with precocious puberty, aged 5, 6, and 8 years, received MRL/41 continuously in doses of 50 and 125 mg. per day for 4 to 5 months. The 8-year-old child received the medication for 5 months. She ultimately showed a lessening in the amount of menstrual flow, regression of vaginal cytologic response, and some decrease in breast size. However, she became rebellious and irritable, and medication was discontinued. In the other 2 girls, regressive changes in the vaginal cytology were also noted.

Result of MRL/41 Administration to 43 Amenorrheic Women

Number of Cases			Resultant Ovulatory Menses
3		Primary amenorrhea	0*
11	36	Secondary amenorrhea	7
14		Functional amenorrhea	11
2		Amenorrhea-menorrhagia syndrome	0
9		Stein-Leventhal and "Steinoid" syndrome	5
4		Premature menopause	0
43			28

* Anovulatory menses occurred in 2 patients; in the other a diagnosis of ovarian agenesis precluded any possibility of a response.

Amenorrheic Women.—This group comprised 43 women complaining of primary, secondary, and functional amenorrhea and amenorrhea associated with hirsutism. Four of the secondary amenorrheics were considered to have premature menopause because of very high urinary gonadotropin titers and hypoesterogenic vaginal cytology. Several of the hirsute women were classified as having the Stein-Leventhal syndrome. Of this group, 2 had failed to respond to previous wedge resection of the ovaries. Some of the hirsute cases were considered to be "Steinoid" [1] in the sense that they complained of amenorrhea, hirsutism, and infertility but did not have demonstrably enlarged ovaries. A classification of cases and the number responding to one or more trials of therapy, as indicated by an ovulatory rise in BTR with ensuing menses, is recorded in the table.

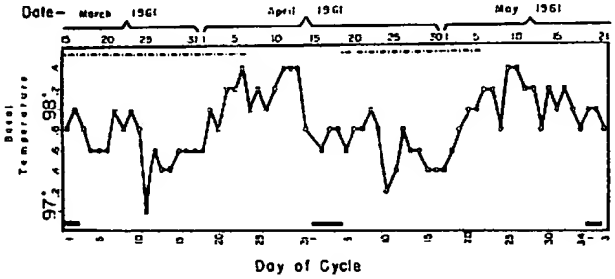

Fig. 1—Induction of ovulatory menstrual periods with MRL/41. Medication was stopped a few days after thermogenic shift in basal temperature. Solid line at bottom indicates menses; dot-and-dash line at top indicates administration of 50 mg. of MRL/41 per day.

Several women continued to menstruate cyclically after MRL/41 was discontinued; in others, ovulatory-type menses failed to occur when therapy was interrupted. In some cases therapy was discontinued soon after the thermogenic shift and the luteal phase proceeded normally (Fig. 1). Four patients in our series have received cyclic MRL/41 for 6 to 8 months with an ovulatory-type response occurring with each course of medication. A detailed report of one such case follows.

Report of a Case

A well-nourished, intelligent white woman aged 23 years was first seen some 6 years ago because of secondary amenorrhea. Menarche was established at 13 years of age, but menses were irregular and scanty until age 16. When she was first studied at age 17, excretory rates for urinary 17-ketosteroids and 17-hydroxycorticoids were 11.4 and 4.0 mg. in 24 hours respectively. The rate for urinary gonadotropins was between 6.6 and 52 mouse units (normal). The serum cholesterol level was 150 mg.%, and the protein-bound iodine (PBI) level was 2.74 mcg.%. Roentgen studies of the sella turcica were normal. Studies of vaginal cytology revealed a mildly hypoestrogenic smear.

The patient was placed on thyroid medication because of the low PBI value and cyclic courses of an estrogen-progesterone preparation were administered, which induced withdrawal menstruation with regularity. After discontinuing hormone therapy, she experienced only a very occasional menstrual period. Prednisolone in a dosage of 7.5 mg. per day along with 25 mcg. of l-triiodothyronine was then tried for a period of 5 months. Menstruation occurred only once during this time. On another occasion conjugated estrogenic substances (Premarin) were given intravenously for 2 consecutive days, but this procedure also failed to induce ovulation.

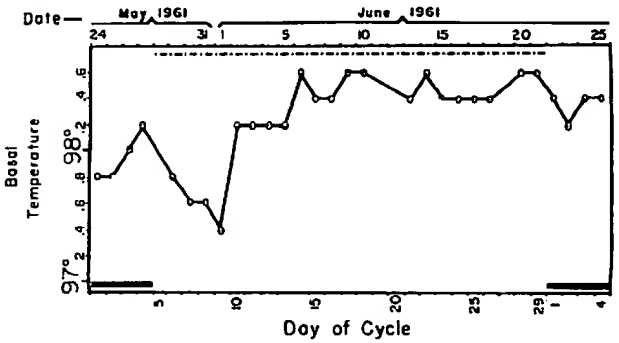

Fig. 2—Induction of ovulatory menstrual period with MRL/41. Note sustained corpus luteum effect on the thermogenic response while on medication from day after cessation to start of menses. Solid line at bottom indicates menses; dot-and-dash line at top indicates administration of 25 mg. of MRL/41 three times a day.

MRL/41 therapy was instituted in November, 1960, and an ovulatory-type menstrual cycle resulted. The treatment was withheld for the following month, and menses failed to occur. A 5-day course of an oral progestogen was given to induce a withdrawal menstrual period. From January to July, 1960, 6 consecutive ovulatory-type cycles, each lasting about 30 to 34 days, followed the administration of 75 mg. of MRL/41 daily during the intermenstruum. It is interesting to note that the thermogenic shift occurred at about the 10th or 11th day of the cycle and that the elevation in BTR persisted to and frequently through the ensuing menstrual period (Fig. 2). Studies performed on day 20 of her last treated cycle revealed that the cervical mucus failed

to fern, the vaginal cytology was luteal, and the endometrium was in the secretory phase. Incidentally, when medication was withheld for 30 days after the July menstrual period, the basal temperature record remained uniphasic and anovulatory.

Untoward Effects

Several untoward effects were noted with MRL/41 therapy. In one patient, a general rash developed and medication was discontinued. In another, swelling of the eyelids occurred for 2 consecutive months with the onset of menses. Since this patient experienced painful menses for the first time following administration of MRL/41, the swelling could have been a manifestation of severe menstrual molimina. The reaction, except for the dysmenorrhea, did not recur with succeeding courses of therapy.

Hot flashes were the most common complaint. These occurred in 7 cases.

In one patient, ovarian cysts estimated to be 5 to 6 cm. in diameter were palpable on pelvic examination after each of 2 courses of MRL/41. There was a prolonged elevation of the BTR in each instance, and an endometrial biopsy obtained during this phase proved to be secretory. In 2 other cases cystic ovaries developed which were palpable and which regressed slowly.

Laboratory Studies

Hormonal assays for urinary 17-ketosteroids and 17-ketogenic steroids showed no evidence of adrenal suppression by this drug. In several cases normal values for urinary pregnanediol were obtained during the luteal phase of the cycle. Endometrial biopsies obtained during this phase showed progestational changes in 9 of the 10 instances. In one, the endometrial tissue was scanty and revealed a mixed endometrium with poor secretory response during the first trial of therapy, but subsequently responded with a good secretory phase on a second course of medication. The high urinary gonadotropin titers found in the 4 cases of premature menopause were not appreciably altered by MRL/41, nor was there any significant change in the vaginal cytology or cervical mucus in these patients.

Comment

The suppressing effect of MRL/41 on ovulation and fecundity in the rat was shown by Holtkamp et al.,[4] and the antifertility action of this drug in male and female rats was reported by Segal and Nelson.[5] Therefore, it is surprising that our observations of the human female suggest that MRL/41 is capable of inducing ovulatory-type menstruation. Another phase of this drug's activity which needs clarification is the sustained thermogenic response, which in many instances lasted for more than 14 days. It may be surmised that the induction and persistence of the corpus luteum effect by MRL/41 is due to a modifying influence on the gonadotropic mechanisms of the pituitary gland. Maintenance of the corpus luteum is a luteotropic effect and may also be produced if large doses of chorionic gonadotropin are administered during the luteal phase of the cycle.[6]

Induction of ovulation in the human has been of considerable research interest for several decades. Administration of human follicle-stimulating hormone (FSH) when followed by human chorionic gonadotropin (HCG) has been known to induce ovulation.[7] This method is not likely to come into general use because of the scarcity of human FSH.[8-10] Glucocorticoids have some merit in anovulatory women,[11] particularly in certain hirsute amenorrheic women.[12] Wedge resection of the ovaries has proved a valuable procedure in the management of the Stein-Leventhal syndrome [13] through the reduction of ovarian mass.[14] Occasionally, cyclic estrogen and progesterone have been used successfully in functional amenorrhea to restore pituitary-ovarian balance. Striking results are frequently obtained with thyroid medication in the subclinical hypothyroid patient with ovulatory failure. Radiation therapy of the pituitary gland and the ovaries has its protagonists, and successes have been reported with stimulating doses.[13]

An antiestrogen property for MRL/41 is suggested by the induction of hot flashes in several cases. In 3 children with precocious puberty who received prolonged MRL/41 therapy, regression of the vaginal cytology from estrogenic to hypoestrogenic was noted along with some decrease in size of the breasts. That MRL/41 in the dosages employed is not an antifertility agent may be readily surmised from the fact that 4 patients in our series are now pregnant. In 2 of these patients medication was taken throughout the cycle in which conception occurred. Of the other 2 patients, medication in one was stopped 10 days before a delayed ovulation occurred, and in the remaining case cyclic menses occurred after regulation with MRL/41, and conception occurred 3 months later. In still another case, a false pregnancy must be presumed, since positive pregnancy tests were obtained on 2 occasions. Then mild spotting began and continued for several weeks, after which the basal temperature remained elevated but the tests for pregnancy became negative.

Although the mechanism of action of this compound is not clear at the present time, it is heartening to find a drug which holds much promise of inducing ovulatory-type menses with considerable regularity in anovulatory amenorrheic women. The finding of antifertility effects in experimental animals cannot be equated with our findings in human females, and this divergence is indeed puzzling. It may be that much larger doses than those used in our studies would have antifecundity

properties in the human. Further clinical and experimental studies are needed to unravel the various biological actions of this drug.

Conclusions

1. MRL/41, an analogue of a nonsteroid estrogenic substance, chlorotrianisene (Tace), appears to have a wide spectrum of biologic activity. No toxic reactions of hematopoietic, renal, or hepatic function have thus far been detected.

2. MRL/41 is not a progesterone-like substance. This may be deduced from the fact that the thermogenic response was noted only in the luteal phase of the cycle in spite of continuous administration of the compound.

3. An antiestrogenic effect has been suggested by the occurrence of hot flashes in quite a few patients and by the fact that regressive changes took place in the vaginal mucosa in children with precocious puberty. Androgenic manifestations were not noted in any instance.

4. The salient feature of this drug is its apparent ability to modify pituitary-ovarian balance in the human with resultant induction of ovulatory-type menses. Such an action was evidenced by the secretory changes in the endometrium, the inhibition of ferning of cervical mucus, and the sustained corpus luteum effect, as noted by the prolonged thermogenic response before the onset of menstruation.

5. Twenty-eight of 36 patients (77.7%) with functional or secondary amenorrhea or amenorrhea associated with hirsutism responded satisfactorily to courses of MRL/41.

The MRL/41 used in this study was supplied by Dr. Carl Bunde through the scientific laboratories of the Wm. S. Merrell Company.

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STERILIZATION OF INTERPLANETARY VEHICLES.—The National Aeronautics and Space Administration is actively investigating means of preventing extraterrestrial biological contamination. In this undertaking it has enlisted the cooperation of the U. S. Army Chemical Corps, through a government interagency agreement, because of the Chemical Corps' considerable success in developing techniques for the sterilization of unusual objects ranging from delicate laboratory equipment to rugged 6 by 6 Army trucks. The Russian Government, apparently, is similarly concerned. It was announced over Radio Moscow that the probe which the Russians landed on the moon just prior to Khrushchev's visit to this country had been sterilized!—C. R. Phillips and R. K. Hoffman: Sterilization of Interplanetary Vehicles, *Science*, Oct. 14, 1960.